Mechanism of Injury Affects Acute Coagulopathy of Trauma in Combat Casualties

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Background: Recent evidence suggests trauma involving total body tissue damage increases the acute coagulopathy of trauma (ACOT) by various mechanisms, especially in massive transfusion (MT). Our hypothesis was that MT patients injured by explosion will have a higher international normalization ratio (INR) at admission than MT patients injured by gunshot wound (GSW).

Methods: A retrospective review was performed on US military injured in Operation Iraqi Freedom/Operation Enduring Freedom from March 2003 to September 2008, who received MT (≥10 red blood cells in 24 hours) and had an INR on admission. Two cohorts were created based on mechanism. Admission vital signs, labs, transfusion, and mortality data were compared.

Results: Seven hundred fifty-one MT patients were identified. Four hundred fifty patients had admission INR and were injured by either GSW or explosion. Patients demonstrated similar injury severity scale and Glasgow Coma Scale. Patients injured by explosion presented with higher INR, greater base deficit, and more tachycardic than patients injured by GSW. Transfusion of blood products was similar between both groups.

Conclusions: The primary finding of this study is that patients injured by explosion presented with a higher INR than those injured by GSW, even with similar injury severity scale. In addition, patients injured by explosion presented more tachycardic and with a greater base deficit. These findings support the theory that ACOT is affected by the amount of tissue injured. Further research is needed into the pathophysiology of ACOT because this may impact care of patients with total body tissue damage/hypoxia and improve the treatment of their coagulopathy while minimizing the attendant complications.

Key Words: Coagulopathy, Massive transfusion, Trauma, Blunt, Penetrating.

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The acute coagulopathy of trauma (ACOT) is a poorly understood yet clinically significant entity relatively new to critical care. ACOT occurs early in the postinjury phase and has been associated with increased transfusion requirements and mortality.[1–3] Initially, the cause of ACOT was believed to be secondary to loss of clotting proteins, dysfunction of coagulation proteins, and dilution from crystalloid resuscitation. This third theorized cause was challenged in a 2003 study by Brohi et al.[1], in which prehospital fluid resuscitation was minimal and yet over a quarter of the trauma patients arrived coagulopathic. This early study led investigators to delve deeper into the preconceived notions regarding the cause of ACOT.

The prehospital treatment of shock consists mainly of crystalloid-based fluid resuscitation. Classically, this had been believed to dilute clotting factors, thereby contributing to coagulopathy. However, work by Brohi et al.[1] has challenged this classical teaching. In their study, there was no association between prehospital fluid administration and incidence of coagulopathy. In addition, *in vitro* and *in vivo* studies on healthy volunteers have found that 1 L of crystalloid had no effect on blood coagulation and 40% to 60% hemodilution was required to induce a coagulopathy.[4,5] These data agree with a German study, which found that more than half of patients who received over 3 L of fluid prehospital arrived coagulopathic.[6] It seems that reasonable amounts of crystalloid do not adversely affect coagulopathy to a clinically relevant level.

Hypothermia is a potentially preventable complication of prehospital treatment and transport and has been associated with increased risk of mortality.[7] It has been implicated as a cause of coagulopathy caused by decreased function of the enzymatic pathways of the coagulation cascade. However, further testing shows little effect on function or clinical bleeding above 33°C.[8–10]

Consumption or loss of coagulation proteins has classically been accepted as the root cause of traumatic coagulopathy.[11] Clotting factors are either used to obtain hemostasis or lost as bleeding. However, without concomitant shock, coagulation does not seem to be deranged.[12]

Although it is difficult to entirely separate the effect of acidemia and tissue hypoperfusion, acidemia has been shown to adversely affect the function of the coagulation cascade. The clinical significance of acidemia on ACOT seems mild for pH greater than 7.2.[9]

All of the above findings support the argument that there is another causative factor in ACOT. This is further supported by the work of Brohi et al.[12] who suggest that there also exists a systemic anticoagulation and hyperfibrinolytic state that accompanies ACOT.[13] The thrombomodulin/activated protein C pathway has been theorized to account for the systemic anticoagulation portion of ACOT. Trauma activates the extrinsic coagulation pathway in an attempt to obtain hemosta-

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sis. When tissue hypoperfusion is present however, the endothelium expresses thrombomodulin, which pushes the coagulation system from an appropriate procoagulant state to an inappropriate anticoagulant state, ultimately leading to activation of protein C and inhibition of the extrinsic pathway. This hypothesis has recently been supported by a study in mice by Chesebro et al.[14] Furthermore, a hyperfibrinolytic state is believed to be a downstream effect of the activation of protein C. It is known that an excess of activated protein C will consume plasminogen activator inhibitor-1.[15] This reduction in plasminogen activator inhibitor-1 is associated with an increase in tissue plasminogen activator and results in systemic hyperfibrinolysis.[12]

Injuries sustained from improvised explosive devices (IEDs) have been a leading cause of morbidity and mortality during Operation Iraqi Freedom and Operation Enduring Freedom. Anecdotal evidence from recent deployed US military surgeons has suggested that patients injured from IED blasts could be more coagulopathic and require more aggressive resuscitation with blood products compared with patients injured from gunshot wounds (GSW).

Shock, or cellular hypoperfusion, seems to be the main driver of early coagulopathy by inducing anticoagulation and hyperfibrinolysis.[12,16] The earliest measure of cellular hypoperfusion available on admission is a cuff systolic blood pressure (SBP). The SBP is used as a surrogate measure of cellular shock. In addition, a base deficit (BD) is typically reported with a venous blood drawn at admission and is a more specific measure of cellular hypoxia.

In general, an explosive mechanism causes an extremely large burden of tissue injury/hypoperfusion compared with a GSW mechanism. This led to the hypothesis that, in massive transfusion (MT) patients, explosion mechanism is associated with a greater coagulopathy than the GSW mechanism.

PATIENTS AND METHODS

A retrospective review of the theater transfusion database was approved by the Brooke Army Medical Center Institutional Review Board. The database includes the majority of US military patients who have received a blood transfusion in Iraq or Afghanistan from March 2003 to September 2008. Data were obtained from the Joint Theater Trauma System transfusion database, the Joint Theater Trauma Registry, and the Joint Patient Tracking Application. The Joint Theater Trauma Registry is a Department of Defense database established to prospectively collect data from multiple clinical and administrative systems. The Joint Patient Tracking Application is a Department of Defense application to record a patient's progress from the battlefield through recovery or death. A retrospective cohort analysis was performed of consecutive patients who required a MT and could either be classified as injured by GSW or explosion.

Demographic, laboratory, and physiologic data, and transfusion requirements, were obtained and outcomes determined. Blood transfusions consisted of packed red blood cells (RBC), plasma (fresh frozen plasma), and platelets, alone or in combination, as well as fresh whole blood (WB). Transfusion requirements were obtained from the transfusion database, and MT was defined as $\geq$10 units of packed RBCs and/or WB in the initial 24 hours after admission. All patients included in the analysis were active duty US military personnel.

Data compiled for analysis included demographic data, mechanism of injury, admission vital signs (VS), admission Glasgow Coma Scale (GCS), admission labs, Injury Severity Scores (ISSs), and mortality. In addition, transfusion requirements during the first 24 hours after admission were obtained. VS and laboratory tests taken on admission were SBP, pulse, GCS, temperature (°F), hemoglobin (Hgb), BD, and international normalization ratio (INR) derived from prothrombin times. Recorded VS and compiled laboratory results were the earliest available after admission. Mechanism of injury was recorded as GSW or explosion. Explosion injuries included IED, mortar, mine, blast, rocket, rocket-propelled grenade, and grenade. Blood values were measured typically using i-STAT (Abbott Point-of-Care, Princeton, NJ). Total transfusion requirements in the first 24 hours after admission included all blood components (units of RBCs, fresh frozen plasma, apheresed platelets, and fresh WB). Individual ISSs were calculated from patient medical records according to published guidelines.[17,18]

Microsoft Office Excel 2003 (Microsoft Corp., Redmond, WA) was used for database construction. Continuous variables were compared with a Student's t test or Wilcoxon test, and categorical variables were described with χ^2 analysis using SPSS 16.0 (Cary, NC). Variables are expressed as mean $\pm$ standard deviation, and statistical significance was set at a p value <0.05.

RESULTS

Seven hundred seventy-seven patients during the study period were identified as receiving a MT, of which 751 patients were either classified as injured by GSW or explosion. One hundred fifty-six patients were injured by GSW, and of those patients, 78 had admission INR data. Five hundred ninety-five patients were classified as injured by explosion. Of those, 372 had INR data. In total, 450 patients were identified who received a MT, were injured by either explosion or GSW, and had INR data.

Patients were similar with regard to age, ISS, SBP, temperature, GCS, Hgb, and mortality (Table 1). The patients injured by explosion presented more tachycardic, with worse BD, and a higher INR compared with the patients injured by GSW. In addition, the incidence of coagulopathy (INR $>$ 1.5) was greater in the explosion cohort (Table 1).

There was no difference in transfusion of RBCs (20 $\pm$ 13 vs. 19 $\pm$ 12, $p = 0.767$), plasma (15 $\pm$ 13 vs. 13 $\pm$ 11, $p = 0.125$), platelets (2 $\pm$ 3 vs. 2 $\pm$ 3, $p = 0.624$), or WB (2 $\pm$ 5 vs. 3 $\pm$ 6, $p = 0.805$) between GSW and explosion injury.

Twenty-nine patients (37%) injured by GSW and 107 patients (29%) injured by explosion presented hypotensive with a SBP $<$90 mm Hg ($p = 0.182$). In the entire study population as a whole and explosion mechanism patients specifically, patients who presented hypotensive had a higher

TABLE 1. Analysis by Cohort

	GSW (N = 78)	Explosion (N = 372)	*p*
Demographics			
Age (yr)	25 ± 6	26 ± 6	0.641
ISS	23 ± 10	24 ± 12	0.291
Vitals			
Pulse	101 ± 36	114 ± 34	0.006
SBP (mm Hg)	100 ± 37	105 ± 36	0.291
Temperature (°F)	97.5 ± 1.9	97.5 ± 6.5	0.999
GCS	11 ± 5	12 ± 5	0.686
Labs			
Hgb (g/dL)	11.7 ± 2.5	11.3 ± 2.8	0.285
BD (mEq/L)	−5.8 ± 6.2	−8.2 ± 7.2	0.006
INR	1.5 ± 0.5	1.8 ± 1.0	<0.001
INR >1.5	37%	50%	0.048
Mortality	24%	21%	0.508

INR than those arriving normotensive (2.1 ± 1.2 vs. 1.6 ± 0.9, $p < 0.01$; 1.9 ± 1.1 vs. 1.6 ± 0.9, $p < 0.01$, respectively). When comparing only those patients who arrived hypotensive, explosion mechanism was associated with a higher INR than GSW (2.1 ± 1.2 vs. 1.6 ± 0.6, $p < 0.01$). Three hundred eighty-seven patients had an admission BD documented. Thirty-eight percent (25 of 65) of patients injured by GSW and 52% (168 of 322) of patients injured by explosion arrived with a BD more negative than −6 mEq/L. Patients who arrived with a BD < −6 mEq/L presented with a higher INR than those who did not in the group as a whole (2.0 ± 1.0 vs. 1.4 ± 0.6, $p < 0.001$), in those injured by GSW (1.7 ± 0.5 vs. 1.3 ± 0.5, $p = 0.010$), and those injured by explosion (2.1 ± 1.1 vs. 1.4 ± 0.6, $p < 0.01$). When comparing only those patients who arrived with a BD < −6 mEq/L, patients injured by explosion had a higher INR than those injured by GSW (2.1 ± 1.1 vs. 1.7 ± 0.5, $p = 0.01$).

DISCUSSION

The primary finding of this study is that patients who were injured by an explosion presented with a higher INR than patients injured by GSW. This is especially significant given that both cohorts had similar ISS, SBP, and GCS. All of the above point to the fact that the severity of injury sustained by these patients was grossly similar. In addition, the incidence of INR >1.5 in both groups ranged from 37% to 50%. This agrees with the observations in both civilian trauma and combat casualties.[1,2,19] The finding that INR was greater in the explosion group than the GSW group is in line with previous arguments that a portion of ACOT is caused by changes at a cellular level secondary to injury/hypoxia and agrees with the contention that ACOT development depends on both injury severity and shock.[12,19]

Although this study does not have data on prehospital fluid resuscitation for these patients, combat medics are trained to resuscitate to restoration of pulse or improved mentation and carry a limited amount of crystalloid. Therefore, there would likely not be a difference in the amount of prehospital resuscitation received between the two groups. In addition, any difference would likely not be clinically relevant based on the amount of crystalloid needed to affect the coagulation system.[6]

The admission temperature was similar between both groups. The group as a whole had a 23% incidence of hypothermia, with 21.5% mild (<36°C), 1.3% moderate (<34°C), and 0% severe (<32°C). This is similar to previous findings of the incidence of hypothermia during combat operations and in civilian trauma systems.[7,20,21] The similarity in the two groups with regard to their admission temperature effectively eliminates the impact of hypothermia on ACOT in our study.

Hgb is an indirect measure of the loss of blood, and therefore, clotting proteins, and was similar between both groups in our study. This finding is likely multifactorial and includes limited prehospital crystalloid use and the fielding of tourniquets to every soldier and their documented use.[22,23]

The patients in the explosion group presented with a greater BD, a surrogate marker of tissue hypoperfusion and shock. This was not unexpected given that acidemia and cellular hypoxia are frequently covariants and supports our argument that changes at a cellular level are important in the pathophysiology of ACOT.

The importance of the shock state's influence on ACOT is evident in our results. Patients who presented with a BD <-6 mEq/L and those who presented hypotensive (SBP < 90 mm Hg) had a higher an INR at admission. BD <-6 mEq/L was associated with an increased incidence of coagulopathy (55% vs. 22%, $p < 0.001$). Hypotension at admission was also associated with an increased incidence of coagulopathy (52% vs. 34%, $p < 0.001$).

Patients received similar amounts of blood products in the first 24 hours after presentation. This is not surprising given that we selected a severely injured subset of patients for this study. The mortality rate between the groups was similar. A subset of seriously injured patients was selected as demonstrated by a mean ISS of 24. It is therefore not surprising that an extremely gross outcome measure such as mortality was similar between the two cohorts.

This study has the inherent limitations of a retrospective study and is restricted by available data collected during the study period. Regardless, the data suggest that the amount of tissue damaged by trauma has an effect on ACOT.

In conclusion, patients injured by explosion have a greater ACOT than those injured by GSW. This association suggests that the explosive mechanism causes a degree of diffuse tissue injury, which cannot be assessed by a gross injury scale such as the ISS. This diffuse microscopic tissue injury may contribute to the ACOT seen in these patients, which is manifested as tachycardia, shock, and coagulopathy. Further research is needed to elucidate the exact mechanisms behind ACOT and develop novel treatment regimens that will maximize early attenuation of the coagulopathy and prevent the late hypercoagulability and increased thrombotic risk associated with ACOT.

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